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EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 08/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/890,297	VAN URK ET AL.	
	Examiner	Art Unit	
	Teresa E. Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-56,59-92 and 95-151* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-56,59-92 and 95-151* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to an amendment filed May 18, 2006. Claims 54-56, 59-92 and 95-142 were previously pending. Applicants amended claims 54, 76, 79, 82, 83, 86, 87, 90, 111, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134-142, and added new claims 143-148. Claims 54-56, 59-92 and 95-148 are pending and will be examined.

2. Applicants' amendments overcame the following rejections: rejection of claims 54-56, 61, 63-65, 74-81, 90-92, 96, 98-100, 109-115, 134-136, 141 and 142 under 35 U.S.C. 102(b) as being anticipated by Matsuoka et al. as evidenced by Cohn et al. and Shaklai et al.; rejection of claims 59-62 and 95-97 under 35 U.S.C. 103(a) as being unpatentable over Matsuoka et al. (as evidenced by Cohn et al., Shaklai et al. and Ohmura et al.) and Goodey et al.; rejection of claims 116-121 and 130-133 under 35 U.S.C. 103(a) over Matsuoka et al. (as evidenced by Cohn et al. and Shaklai et al. and Ohmura et al.). All other previously presented rejections are maintained for reasons given in the "Response to Arguments" section below.

3. The declaration of Philip Morton under 37 CFR 1.132 filed May 18, 2006 is insufficient to overcome the rejections as set forth in the last Office action for reasons given in the "Response to Arguments" section below.

4. This office action contains new grounds for rejection which were necessitated by amendment.

Response to Arguments

5. Applicant's arguments filed May 18, 2006 have been fully considered but they are not persuasive. Only arguments pertinent to the still-pending and new rejections will be addressed.

A) Regarding the Matsuoka et al. and Goodey et al. references, Applicants argue the following:

a) Matsuoka et al. do not teach purification of a recombinantly produced albumin, and the glycosylated albumin of Matsuoka et al. is not enzymatically glycosylated, therefore it is a physically different compound, and Matsuoka et al. do not teach removal of glycosylated albumin by cation exchange.

b) A recombinant albumin solution contains different types and levels of contaminants as compared to the solution of albumin obtained from plasma, therefore one would not be motivated to use the method of Matsuoka et al. to purify a recombinant protein, especially since Goodey et al. teach away from using CE in a negative mode with respect to albumin.

c) It would not be obvious to use octanoate in a solution which was subject to cation exchange chromatography, in view of Applicants' unexpected results of obtaining increased yield of albumin (also in the declaration of Philip Morton).

d) Albumin polymerization would not be problematic during purification on a CE column run in the negative mode with respect to albumin, since the albumin would not be "at risk" for polymerization.

e) Applicants present unexpected results of using albumin concentration subjected to CE chromatography in the range of 20-250 g/L or 50±10 g/L, in that as the loading concentration of albumin increases its yield increases as well and the contamination level decreases.

Regarding a), as noted by Applicants on page 45, lines 4-16, albumin is inherently glycosylated by being overexpressed in yeast cells. Goodey et al. teach production of recombinant albumin from yeast cells, therefore they inherently teach having glycosylated albumin in their preparations. Even if it were true that the enzymatically and non-enzymatically glycosylated albumins have different structures of the sugar chains, the bottom line would be that their charge properties would be similar, therefore, they would be inherently removed on the CE column of

Matsuoka et al. Further, as explained in the previous office actions, the fact that an inherent feature was not recognized at the time of the invention, does not prevent anticipation of the tresults. Finally, only claims 55, 77, 80, 91, 112 and 134-142 are drawn to the presence of glycosylated albumin.

Regarding b), Goodey et al. do not teach away from using negative mode cation exchange, they simply do not teach it, which is quite different. Nowhere in the Goodey et al. reference there is a statement "CE run in the negative mode with respect to albumin should not be used..." or some similar statement.

Regarding c), Applicants' arguments and the declaration of Philip Morton are not convincing as to the unexpected results of using octanoate. First, the octanoate concentrations presented in the table are in units of mole/mole, and it is not clear what these units mean. Is it moles of octanoate per moles of protein, or per moles of buffer? It is not clear how these relate to the claimed octanoate concentrations of 2-15 mM or 5-10 mM. Further, the declaration does not specify what was the albumin concentration for which these data points were obtained. In conclusion, this arguments is not considered to be persuasive.

Regarding d), Applicants claim using octanoate for the range of albumin concentrations of 10-250 g/L, which, at the lower range, has no danger of polymerization either. Further, Goodey et al. use the octanoate to elute albumin from a column to which it binds, therefore, they use it for the purpose of specific binding to albumin.

Regarding e), Applicants' arguments and the declaration of Philip Morton are not persuasive with respect to unexpected results of increased albumin recovery and decreased levels of contaminants in the purified albumin. First, Applicants claim the range of 10-250 g/L of albumin concentrations loaded onto the CE column, but the declaration provides only four concentrations: 5,

25, 50 and 100 g/L, which is not commensurate with the scope of the claims. As can be seen at the highest albumin concentration of 100 g/L, the contaminant level has actually decreased from the 50 g/L sample. As no other albumin loading concentrations were presented, it is not clear if the trend of increasing contaminant level continues with an increase of albumin loading concentration. Therefore, Applicants' declaration is ineffective in overcoming the rejections.

Regarding the concentration of albumin applied to the CE column of Matsuoka et al., examiner thanks the Applicants for correcting the error in calculating the albumin concentration loaded onto the CE column of Matsuoka et al. However, even if the concentration was lower by another 30% or so, it still is above 10 g/L, which is a lower range claimed by Applicants.

Claim Interpretation

6. Before proceeding with art rejections meaning of some of the terms present in the claims, for which the definitions were not provided by Applicants, will be interpreted. "Chromatography in the negative mode with respect to albumin" is interpreted to mean that albumin is not adsorbed onto the chromatographic matrix and is recovered in the flow-through, and "chromatography in the positive mode with respect to albumin" is interpreted to mean that albumin is adsorbed onto the chromatographic matrix. The term "initial albumin solution" is interpreted as the albumin solution before any of the purification steps. The term "glycoconjugate" is interpreted as any glycosylated material, such as glycoproteins, glycopeptides, etc.

7. A note regarding rejection of the claims in which the order of steps was reversed: reversal of steps is considered to be prima facie obvious (see MPEP 2144.04 IV C), therefore claims in which the only difference is reversal of steps will be rejected together, for example, claims 54-75 and 90-110, claims 76-78 and 79-81, claims (82, 84) and (86, 88), claims (83, 85 and 87, 89).

MPEP 2144.04 IV C. Changes in Sequence of Adding Ingredients

Ex parte Rubin , 128 USPQ 440 (Bd. App. 1959) (Prior art reference disclosing a process of making a laminated sheet wherein a base sheet is first coated with a metallic film and thereafter impregnated with a thermosetting material was held to render prima facie obvious claims directed to a process of making a laminated sheet by reversing the order of the prior art process steps.). See also In re Burhans, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) (selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results); In re Gibson, 39 F.2d 975, 5 USPQ 230 (CCPA 1930) (Selection of any order of mixing ingredients is prima facie obvious.).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 54-56, 59-67, 69-71, 74-81, 90-92, 95-102, 104-106, 109-115, 134-136, 141 and 142 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodey et al. (WO 97/31947; cited in the IDS and in the previous office action) and of Matsuoka et al. (EP 0 428 758; cited in the IDS) (as evidenced by Cohn et al. (J. Am. Chem. Soc., vol. 68, pp. 459-475, 1946), Shaklai et al. (J. Biol. Chem., vol. 259, pp. 3812-3817, 1984; cited in the previous office action) and Ohmura et al. (EP 0 570 916 A2; cited in the IDS and in the previous office action)).

A) Regarding claims 54 and 90, Goodey et al. teach a process for purifying an albumin solution, the process comprising:

(1) subjecting the albumin solution to cation exchange (CE) chromatography in the positive mode with respect to albumin in order to yield an albumin-containing CE product (Goodey et al. teach CE chromatography of an albumin solution on cation exchanger; see page 1, lines 26-31; page 2, lines1-10);

(2) subjecting the albumin-containing CE product, with or without intervening purification step, to anion exchange (AE) chromatography to yield an albumin-containing AE product (Goodey et al. teach a process comprising CE and AE chromatography, with a possible steps of affinity chromatography (AC), ultrafiltration and gel permeation chromatography before AE chromatography; see page 2, lines 6-31; page 3, lines 1-16);

(3) placing the albumin-containing AE product, without further purification, into a final container for therapeutic use (Goodey et al. teach placing the purified albumin into a plurality of vials (page 6, lines 28-30) and placing the albumin solution into a bulk product formulation vessel, followed by completing formulation by addition of pharmacetutically acceptable excipients (page 27, lines 20-22).);

wherein the albumin solution is a recombinant albumin solution (Goodey et al. teach expressing albumin in yeast cells (page 6, lines 15-26).)

Regarding claims 55, 77, 80, 91, 112, 134-136, 141 and 142, Goodey et al. do not specifically teach that albumin contains glycosylated albumin and that it binds during the cation exchange step. As evidenced by Applicants (page 45, lines 4-16), albumin produced in yeast is glycosylated, therefore by teaching recombinant albumin produced in yeast Goodey et al. inherently teach glycosylated albumin.

II. INHERENT FEATURE NEED NOT BE RECOGNIZED AT THE TIME OF THE INVENTION

> There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure *at the time of invention*, but only that the subject matter is in fact inherent in the prior art reference. ... *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343-44, 74 USPQ2d 1398, 1406-07 (Fed. Cir. 2005) (holding that a prior art patent to an anhydrous form of a compound "inherently"

anticipated the claimed hemihydrate form of the compound because practicing the process in the prior art to manufacture the anhydrous compound "inherently results in at least trace amounts of" the claimed hemihydrate even if the prior art did not discuss or recognize the hemihydrate)<.

Regarding claims 59, 60 and 95, Goodey et al. teach treating initial albumin solution with octanoate concentration of 1-10 mM (page 3, lines 20-22; page 16, lines 9-11).

Regarding claims 61, 62, 96 and 97, Goodey et al. teach adjusting the pH of albumin solution and conditioning of albumin solution by addition of octanoate salt prior to cation exchange step (page 3, lines 20-22; page 16, lines 9-11).

Regarding claims 63 and 98, Goodey et al. teach AE step utilizing a matrix such as DEAE-Spherodex, Q-Hyper D, DEAE-cellulose, QAE-cellulose, TMAE, DMAE, DEAE Fractogel or DEAE Sepharose FF (page 25, lines 12-14). Goodey et al. do not specifically teach dialkylaminoalkyl subsituents as anion exchangers. As evidenced by Ohmura et al., DEAE means diethylaminoethyl group (page 6, lines 11-15), which is a species of dialkylaminoalkyl groups (Lindquist et al., col. 3, lines 53-56). Therefore, since Goodey et al. teach DEAE-Spherodex, DEAE Fractogel or DEAE Sepharose FF, they teach dialkylaminoalkyl subsituents as anion exchangers.

Regarding claims 66 and 101, Goodey et al. teach that solution undergoing anion exchange chromatography has a conductivity of less than 4 mS/cm, namely, 2.5 $\pm$ 0.5 mS/cm (page 32, lines 1, 2).

Regarding claims 67 and 102, Goodey et al. teach AE step run in a positive mode with respect to albumin (page 25, lines 9-29).

Regarding claims 69 and 104, Goodey et al. teach ultrafiltration of albumin solution to a

concentration between 20-120 g/L or 80-110 g/L before loading onto AE column (page 24, lines 20-24).

Regarding claims 70 and 105, Goodey et al. teach AE column equilibrated with a buffer with conductivity in the range of 1-4 mS/cm or 1.5-5 mS/cm (page 25, line 20; page 32, line 1).

Regarding claims 71 and 106, Goodey et al. teach elution of albumin from CE column with a solution of octanoate (page 31, lines 21-25), which has specific activity for albumin (page 2, lines 1-4). Goodey et al. do not teach elution of albumin from AE column using a solution of octanoate. However, they teach that pH of the eluting solution should be about 5.5, so that the binding of octanoate causes a significant overall charge difference (page 31, lines 23, 24). They also teach loading the eluate from the cation exchanger onto AE column equilibrated with a buffer of pH 5.5 (page 31, lines 27-29).

Regarding claims 75 and 110, Goodey et al. teach using cells from the fermenter, therefore they teach primary separation of albumin from other cell components (page 15, lines 10-30).

B) Goodey et al. do not teach albumin purification using CE or AE chromatography run in a negative mode with respect to albumin.

C) Matsuoka et al. teach albumin purification using CE and AE chromatography (Abstract).

Regarding claims 54 and 90, Matsuoka et al. teach a process for albumin purification (Abstract), the process comprising:

(1) subjecting the albumin solution to cation exchange (CE) chromatography in the negative mode with respect to albumin in order to yield an albumin-containing CE product (Matsuoka et al. teach contacting the albumin solution to be purified with a CE exchange matrix to remove proteins having isoelectric points higher than that of albumin, to yield an albumin-containing flow-through (page 3, lines 25-52; page 4, lines 51-57).);

(2) subjecting the albumin-containing CE product, with or without intervening purification step, to anion exchange (AE) chromatography to yield an albumin-containing AE product (Matsuoka et al. teach contacting the albumin solution to be purified with an AE exchange matrix to remove proteins having isoelectric points below that of albumin (page 2, lines 53-55; page 3, lines 1-24; page 4, lines 41-48).);

wherein the albumin solution subjected to cation exchange chromatography in step (1) has an albumin concentration of 10-250 g/L (Matsuoka et al. teach dissolving of 500 g of Cohn fraction V in 4L of solution, loading the solution onto an anion exchange column, recovering the flow-through and adding 2 liters to it before it was loaded onto a cation exchange column (page 4, lines 34-48). As evidenced by Cohn et al., fraction V is about 96% albumin (page 471, 10th paragraph), and that fraction V contains about 250 g/L of protein. Assuming the density of the solution to be about 1 g/mL, 500 g of fraction V would contain therefore contain about 125 g of albumin, which, diluted to 6 L, would yield an albumin concentration of about 20 g/L, anticipating Applicants' range of 10-250 g/L.

Regarding claims 55, 77, 80, 91, 112, 134-136, 141 and 142, Matsuoka et al. do not specifically teach that albumin contains glycosylated albumin and that it binds during the cation exchange step. As evidenced by Shaklai et al., 10% of albumin present in human plasma is glycosylated (Abstract). Therefore, since Matsuoka et al. teach subjecting the albumin to the same purification steps as the ones performed by Applicants, they inherently teach binding of the glycosylated albumin to the cation exchange resin (see MPEP 2112-II):

II. INHERENT FEATURE NEED NOT BE RECOGNIZED AT THE TIME OF THE INVENTION

> There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure *at the time of invention*, but only that the subject matter is in fact inherent in the prior art reference. ... *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343-44, 74 USPQ2d 1398, 1406-07 (Fed. Cir. 2005) (holding that a prior art patent to an anhydrous form of a compound "inherently" anticipated the claimed hemihydrate form of the compound because practicing the process in the prior art to manufacture the anhydrous compound "inherently results in at least trace amounts of" the claimed hemihydrate even if the prior art did not discuss or recognize the hemihydrate)<.

Regarding claims 74, 76 and 135, Matsuoka et al. teach subjecting the anion-exchange product to pH-adjustment (page 4, lines 46-48).

Regarding claim 79, 111, 136 and 142, Matsuoka et al. teach subjecting the cation-exchange product to concentration (page 4, lines 57, 58).

Regarding claims 56 and 92, Matsuoka et al. teach CE step utilizing a matrix such as SP-Sepadex (page 3, line 30, 31). Matsuoka et al. do not specifically teach sulfopropyl subsituents as cation exchangers. As evidenced by Ohmura et al., SP stands for a sulfopropyl group, for example, SP-Sephadex is sulfopropyl-dextran (page 5, lines 37-40). Since Matsuoka et al. teach SP-Sepadex, they inherently teach sulfoprpyl groups as cation exchangers.

Regarding claims 61, 78, 81, 96, 109 and 113, Matsuoka et al. teach adjusting the pH of the albumin solution to 5.5 before loading onto CE column (page 3, lines 46-48).

Regarding claims 63 and 98, Matsuoka et al. teach diethylaminoethyl groups as anion exchangers (page 3, line1), therefore they teach dialkylaminoalkyl anion exchangers.

Regarding claims 64 and 99, Matsuoka et al. teach AE step run in a negative mode with respect to albumin (page 4, lines 42-48).

Regarding claims 65 and 100, Matsuoka et al. teach that albumin solution, which undergoes

AE chromatography has a pH of 5.1 (page 4, lines 37, 38).

Regarding claims 114 and 115, Matsuoka et al. teach albumin solution of pH of about 4.5 to 5.5 loaded onto CE column (page 4, lines 46-48), therefore Matsuoka et al. teach pH within the range of 4.5-6.0.

It would have been *prima facie* obvious to one of ordinary skill in the art to add the CE and AE chromatography steps run in a negative mode with respect to albumin of Matsuoka et al. to the albumin purification method of Goodey et al. The motivation to do so, provided by Matsuoka et al., would have been that using ion exchange in negative mode with respect to albumin resulted in efficient albumin purification with reduced amount of contaminating proteins which lead to polymer formation during heat treatment (page 2, lines 27-32). The teaching of Matsuoka et al. regarding the anion exchange purification therefore enhances the ability of Goodey et al. to obtain highly purified albumin therapeutic treatments (Goodey et al., page 1, lines 1-25).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have eluted albumin from AE column with a buffer containing a compound having a specific affinity for albumin. The motivation to do so would have been that albumin elution could be accomplished with more specificity and efficiency, since no other proteins bound to a compound with specific affinity for albumin.

10. Claims 68, 72, 73, 103, 107 and 108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodey et al. (WO 97/31947; cited in the IDS and in the previous office action) and Matsuoka et al. (EP 0 428 758; cited in the IDS) (as evidenced by Cohn et al. (J. Am. Chem. Soc., vol. 68, pp. 459-475, 1946), Shaklai et al. (J. Biol. Chem., vol. 259, pp. 3812-3817, 1984; cited in the previous office action) and Ohmura et al. (EP 0 570 916 A2; cited in the IDS and in the previous office action)), as applied to claims 67, 71, 102 and 106 above, and further in view of

Ohmura et al. (EP 0 570 916 A2; cited in the IDS and in the previous office action) and Chang (EP 0 422 769 A1; cited in the IDS and in the previous office action).

A) Claim 68 is drawn to a process according to claim 67 wherein the albumin solution which undergoes positive mode anion exchange chromatography has a pH of 6.0-8.0, and claim 73 is drawn to the process according to claim 67 wherein the albumin is eluted in the anion exchange step with a buffer of pH 6.0-8.0. Claim 103 is drawn to a process according to claim 102 wherein the albumin solution which undergoes positive mode anion exchange chromatography has a pH of 6.0-8.0, and claim 108 is drawn to the process according to claim 102 wherein the albumin is eluted in the anion exchange step with a buffer of pH 6.0-8.0. Claim 72 is drawn to a process of claim 71 wherein the buffer comprises 20-90 mM phosphoric acid salt, and claim 107 is drawn to a process of claim 106 wherein the buffer comprises 20-90 mM phosphoric acid salt.

B) Neither Goodey et al. nor Matsuoka et al. teach albumin solution which undergoes positive mode anion exchange chromatography with a pH of 6.0-8.0, or the albumin being eluted in the anion exchange step with a buffer of pH 6.0-8.0. Goodey et al. do not teach albumin elution buffer comprising 20-90 mM phosphoric acid salt.

C) Ohmura et al. teach purification of albumin comprising AE chromatography step run in a positive mode with respect to albumin (page 6, lines 21-24). They teach that albumin can be adsorbed onto AE column using a phosphate buffer of pH 6 to 8 and salt concentration of 0.001-0.05 M, and eluted from the column using buffer with the same pH range and salt concentration of 0.05 to 1 M (page 6, lines 18-24). They teach anion exchange column buffer of 50 mM phosphate (page 11, lines 49-51). Chang teaches albumin purification comprising a step of AE chromatography (Abstract). Chang teaches that at pH > 6.1 albumin becomes more readily bound to the anion exchange column (page 4, lines 31-33).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used a buffer with a pH of 6.0-8.0 of Ohmura et al. in the combined albumin purification method of Goodey et al. and Matsuoka et al. The motivation to do so, provided by Chang, would have been that at pH > 6.1 albumin bound better to AE column than contaminating proteins (page 4, lines 31-33).

11. Claims 82, 84, 86, 88, 137 and 139 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodey et al. (WO 97/31947; cited in the IDS and in the previous office action) and Matsuoka-1 et al. (EP 0 428 758; cited in the IDS) (as evidenced by Cohn et al. (J. Am. Chem. Soc., vol. 68, pp. 459-475, 1946) and Shaklai et al. (J. Biol. Chem., vol. 259, pp. 3812-3817, 1984; cited in the previous office action)) and Matsuoka-2 et al. (U.S. Patent No. 5,277, 818).

A) Regarding claims 82, 86, 137 and 139, Goodey et al. teaches a process for purifying an albumin solution, the process comprising the steps of:

(i) subjecting an albumin solution to a CE chromatography step run in positive mode with respect to albumin (Goodey et al. teach CE chromatography of an albumin solution on cation exchanger; see page 1, lines 26-31; page 2, lines 1-10; page 21, lines 1-26);

(ii) collecting an albumin-containing CE eluate (Goodey et al. teach collecting 6.5 volumes of eluate; page 21, lines 26-28);

(iii) subjecting the CE eluate to an AE chromatography step run in a positive mode with respect to the albumin (Goodey et al. teach AE chromatography run in a positive mode with respect to albumin; page 25, lines 9-26);

(iv) collecting an albumin-containing AE eluate (Goodey et al. teach collecting albumin-containing eluate; page 3, lines 4-16; page 25, lines 27-29);

(v) subjecting the AE eluate to an affinity chromatography (AC) step run in positive mode

with respect to the albumin (Goodey et al. teach AC chromatography of albumin on a column containing a matrix which specifically binds albumin, such as DBA (Delta Blue Agarose) matrix; page 22; page 23, lines 1-20);

(vi) collecting the albumin-containing AC eluate (Goodey et al. teach collecting the AC eluate; page 3, lines 4-16; page 23, lines 16-20).),

wherein the albumin solution is a recombinant albumin solution (Goodey et al. teach expressing albumin in yeast cells (page 6, lines 15-26).)

Regarding claims 137 and 139, Goodey et al. do not specifically teach that albumin contains glycosylated albumin and that it binds during the cation exchange step. As evidenced by Applicants (page 45, lines 4-16), albumin produced in yeast is glycosylated, therefore by teaching recombinant albumin produced in yeast Goodey et al. inherently teach glycosylated albumin.

II. INHERENT FEATURE NEED NOT BE RECOGNIZED AT THE TIME OF THE INVENTION

> There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure *at the time of invention*, but only that the subject matter is in fact inherent in the prior art reference. ... *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343-44, 74 USPQ2d 1398, 1406-07 (Fed. Cir. 2005) (holding that a prior art patent to an anhydrous form of a compound "inherently" anticipated the claimed hemihydrate form of the compound because practicing the process in the prior art to manufacture the anhydrous compound "inherently results in at least trace amounts of" the claimed hemihydrate even if the prior art did not discuss or recognize the hemihydrate)<.

Regarding claims 84 and 88, Goodey et al. teach adjusting the pH of albumin solution and conditioning of albumin solution by addition of octanoate salt prior to cation exchange step (page 3, lines 20-22; page 16, lines 9-11).

E) Goodey et al. do not teach albumin purification using CE or AE chromatography run in a negative mode with respect to albumin.

F) Matsuoka-1 et al. teach albumin purification using CE and AE chromatography (Abstract). Regarding claims 82, 86, 137 and 139, Matsuoka-1 et al. teach a process for albumin purification (Abstract), the process comprising:

(ix) subjecting the albumin solution to CE chromatography in the negative mode with respect to albumin (Matsuoka-1 et al. teach contacting the albumin solution to be purified with a CE exchange matrix to remove proteins having isoelectric points higher than that of albumin, to yield an albumin-containing flow-through (page 3, lines 25-52; page 4, lines 51-57).);

(x) collecting the albumin-containing CE flow through (Matsuoka-1 et al. teach collecting the fluid containing albumin after CE chromatography (page 4, lines 56, 57).);

(xi) subjecting the albumin solution to AE chromatography in the negative mode with respect to albumin (Matsuoka-1 et al. teach contacting the albumin solution to be purified with an AE exchange matrix to remove proteins having isoelectric points below that of albumin (page 2, lines 53-55; page 3, lines 1-24; page 4, lines 41-48).);

(xii) collecting the albumin-containing AE flow through (Matsuoka-1 et al. teach collecting the fluid containing albumin after AE chromatography (page 4, lines 46-48.),

wherein the albumin solution subjected to cation exchange chromatography in step (1) has an albumin concentration of 10-250 g/L (Matsuoka-1 et al. teach dissolving of 500 g of Cohn fraction V in 4L of solution, loading the solution onto an anion exchange column, recovering the flow-through and adding 2 liters to it before it was loaded onto a cation exchange column (page 4, lines 34-48). As evidenced by Cohn et al., fraction V is about 96% albumin (page 471, 10th paragraph), and that fraction V contains about 250 g/L of protein. Assuming the density of the

solution to be about 1 g/mL, 500 g of fraction V would contain therefore contain about 125 g of albumin, which, diluted to 6 L, would yield an albumin concentration of about 20 g/L, anticipating Applicants' range of 10-250 g/L.).

Regarding claims 137 and 139, Matsuoka-1 et al. do not specifically teach that albumin contains glycosylated albumin and that it binds during the cation exchange step. As evidenced by Shaklai et al., 10% of albumin present in human plasma is glycosylated (Abstract). Therefore, since Matsuoka-1 et al. teach subjecting the albumin to the same purification steps as the ones performed by Applicants, they inherently teach binding of the glycosylated albumin to the cation exchange resin (see MPEP 2112-II):

> **II. INHERENT FEATURE NEED NOT BE RECOGNIZED AT THE TIME OF THE INVENTION**
>
> There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure *at the time of invention*, but only that the subject matter is in fact inherent in the prior art reference. ... *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343-44, 74 USPQ2d 1398, 1406-07 (Fed. Cir. 2005) (holding that a prior art patent to an anhydrous form of a compound "inherently" anticipated the claimed hemihydrate form of the compound because practicing the process in the prior art to manufacture the anhydrous compound "inherently results in at least trace amounts of" the claimed hemihydrate even if the prior art did not discuss or recognize the hemihydrate)<.

It would have been *prima facie* obvious to one of ordinary skill in the art to add the CE and AE chromatography steps run in a negative mode with respect to albumin of Matsuoka-1 et al. to the albumin purification method of Goodey et al. The motivation to do so, provided by Matsuoka-1 et al., would have been that using ion exchange in negative mode with respect to albumin resulted in efficient albumin purification with reduced amount of contaminating proteins which lead to

polymer formation during heat treatment (page 2, lines 27-32). The teaching of Matsuoka-1 et al. regarding the anion exchange purification therefore enhances the ability of Goodey et al. to obtain highly purified albumin therapeutic treatments (Goodey et al., page 1, lines 1-25).

G) Neither Goodey et al. nor Matsuoka-1 et al. teach affinity chromatography run in a negative mode with respect to albumin and in positive mode with respect to glyconjugates.

H) Regarding claims 82, 86, 137 and 139, Matsuoka-2 et al. teach albumin purification using ion exchange and affinity chromatography (Abstract). Matsuoka-2 et al. teach removal of α_1-acid glycoprotein (= glycoconugate) from albumin preparation by affinity chromatography run in a negative mode with respect to albumin (col. 3, lines 38-68; col. 4, lines 1-24).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have removed α_1-acid glycoprotein by affinity chromatography of Matsuoka-2 et al. in the method of albumin purification by Goodey et al. and Matsuoka-1 et al. The motivation to do so, provided by Matsuoka-2 et al., would have been that α_1-acid glycoprotein was an impurity having immunosuppressive activity (col. 1, lines 44-46). Therefore, removing α_1-acid glycoprotein from albumin solution according to Matsuoka-2 et al. enhances the ability of Goodey et al. and Matsuoka-1 et al. to obtain highly purified albumin for therapeutic treatments (Goodey et al., page 1, lines 1-25).

12. Claims 83, 85, 87, 89, 138 and 140 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodey et al. (WO 97/31947; cited in the IDS and in the previous office action) and Matsuoka-1 et al. (EP 0 428 758; cited in the IDS) (as evidenced by Cohn et al. (J. Am. Chem. Soc., vol. 68, pp. 459-475, 1946) and Shaklai et al. (J. Biol. Chem., vol. 259, pp. 3812-3817, 1984; cited in the previous office action)), Matsuoka-2 et al. (U.S. Patent No. 5,277, 818) and Chang (EP 0 422 769 A1; cited in the IDS and in the previous office action).

A) Regarding claims 83, 87, 138 and 140, Goodey et al. teaches a process for purifying an albumin solution, the process comprising the steps of:

(i) subjecting an albumin solution to a CE chromatography step run in positive mode with respect to albumin (Goodey et al. teach CE chromatography of an albumin solution on cation exchanger; see page 1, lines 26-31; page 2, lines 1-10; page 21, lines 1-26);

(ii) collecting an albumin-containing CE eluate (Goodey et al. teach collecting 6.5 volumes of eluate; page 21, lines 26-28);

(iii) subjecting the CE eluate to an AE chromatography step run in a positive mode with respect to the albumin (Goodey et al. teach AE chromatography run in a positive mode with respect to albumin; page 25, lines 9-26);

(iv) collecting an albumin-containing AE eluate (Goodey et al. teach collecting albumin-containing eluate; page 3, lines 4-16; page 25, lines 27-29);

(v) subjecting the AE eluate to an affinity chromatography (AC) step run in positive mode with respect to the albumin (Goodey et al. teach AC chromatography of albumin on a column containing a matrix which specifically binds albumin, such as DBA (Delta Blue Agarose) matrix; page 22; page 23, lines 1-20);

(vi) collecting the albumin-containing AC eluate (Goodey et al. teach collecting the AC eluate; page 3, lines 4-16; page 23, lines 16-20),

wherein the albumin solution is a recombinant albumin solution (Goodey et al. teach expressing albumin in yeast cells (page 6, lines 15-26).)

Regarding claims 138 and 140, Goodey et al. do not specifically teach that albumin contains glycosylated albumin and that it binds during the cation exchange step. As evidenced by Applicants (page 45, lines 4-16), albumin produced in yeast is glycosylated, therefore by teaching recombinant

albumin produced in yeast Goodey et al. inherently teach glycosylated albumin.

II. INHERENT FEATURE NEED NOT BE RECOGNIZED AT THE TIME OF THE INVENTION

There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure *at the time of invention*, but only that the subject matter is in fact inherent in the prior art reference. ... *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343-44, 74 USPQ2d 1398, 1406-07 (Fed. Cir. 2005) (holding that a prior art patent to an anhydrous form of a compound "inherently" anticipated the claimed hemihydrate form of the compound because practicing the process in the prior art to manufacture the anhydrous compound "inherently results in at least trace amounts of" the claimed hemihydrate even if the prior art did not discuss or recognize the hemihydrate)<.

Regarding steps (xi) and (xii) of claim 83 (or steps (ix) and (x) of claim 87), these are repeated steps (iii) and (iv). Goodey et al. do not specifically teach repeating AE step in a positive mode with respect to albumin.

Regarding claims 85 and 89, Goodey et al. teach adjusting the pH of albumin solution and conditioning of albumin solution by addition of octanoate salt prior to cation exchange step (page 3, lines 20-22; page 16, lines 9-11).

B) Goodey et al. do not teach albumin purification using CE chromatography run in a negative mode with respect to albumin.

C) Matsuoka-1 et al. teach albumin purification using CE chromatography (Abstract).

Regarding claims 83, 87, 138 and 140, Matsuoka-1 et al. teach a process for albumin purification (Abstract), the process comprising:

(ix) subjecting the albumin solution to CE chromatography in the negative mode with respect to albumin (Matsuoka-1 et al. teach contacting the albumin solution to be purified with a CE

exchange matrix to remove proteins having isoelectric points higher than that of albumin, to yield an albumin-containing flow-through (page 3, lines 25-52; page 4, lines 51-57).);

(x) collecting the albumin-containing CE flow through (Matsuoka-1 et al. teach collecting the fluid containing albumin after CE chromatography (page 4, lines 56, 57).),

wherein the albumin solution subjected to cation exchange chromatography in step (1) has an albumin concentration of 10-250 g/L (Matsuoka-1 et al. teach dissolving of 500 g of Cohn fraction V in 4L of solution, loading the solution onto an anion exchange column, recovering the flow-through and adding 2 liters to it before it was loaded onto a cation exchange column (page 4, lines 34-48). As evidenced by Cohn et al., fraction V is about 96% albumin (page 471, 10th paragraph), and that fraction V contains about 250 g/L of protein. Assuming the density of the solution to be about 1 g/mL, 500 g of fraction V would contain therefore contain about 125 g of albumin, which, diluted to 6 L, would yield an albumin concentration of about 20 g/L, anticipating Applicants' range of 10-250 g/L.).

Regarding claims 138 and 140, Matsuoka-1 et al. do not specifically teach that albumin contains glycosylated albumin and that it binds during the cation exchange step. As evidenced by Shaklai et al., 10% of albumin present in human plasma is glycosylated (Abstract). Therefore, since Matsuoka-1 et al. teach subjecting the albumin to the same purification steps as the ones performed by Applicants, they inherently teach binding of the glycosylated albumin to the cation exchange resin (see MPEP 2112-II):

> **II. INHERENT FEATURE NEED NOT BE RECOGNIZED AT THE TIME OF THE INVENTION**
>
> There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure *at the time of invention*, but only that the subject matter is in fact inherent

in the prior art reference. ... *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343-44, 74 USPQ2d 1398, 1406-07 (Fed. Cir. 2005) (holding that a prior art patent to an anhydrous form of a compound "inherently" anticipated the claimed hemihydrate form of the compound because practicing the process in the prior art to manufacture the anhydrous compound "inherently results in at least trace amounts of" the claimed hemihydrate even if the prior art did not discuss or recognize the hemihydrate)<.

It would have been *prima facie* obvious to one of ordinary skill in the art to add the CE chromatography step run in a negative mode with respect to albumin of Matsuoka-1 et al. to the albumin purification method of Goodey et al. The motivation to do so, provided by Matsuoka-1 et al., would have been that using ion exchange in negative mode with respect to albumin resulted in efficient albumin purification with reduced amount of contaminating proteins which lead to polymer formation during heat treatment (page 2, lines 27-32). The teaching of Matsuoka-1 et al. regarding the anion exchange purification therefore enhances the ability of Goodey et al. to obtain highly purified albumin therapeutic treatments (Goodey et al., page 1, lines 1-25).

D) Neither Goodey et al. nor Matsuoka-1 et al. teach repeating AE chromoatography steps or affinity chromatography run in a negative mode with respect to albumin and in positive mode with respect to glyconjugates.

E) Regarding claims 83, 87, 138 and 140, Chang teaches repeating AE chromatography steps to remove contaminating proteins from albumin solution (Abstract; page 4, lines 17-39).

F) Regarding claims 83, 87, 138 and 140, Matsuoka-2 et al. teach albumin purification using ion exchange and affinity chromatography (Abstract). Matsuoka-2 et al. teach removal of α_1-acid glycoprotein from albumin preparation by affinity chromatography run in a negative mode with respect to albumin (col. 3, lines 38-68; col. 4, lines 1-24).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have removed α_1-acid glycoprotein by affinity chromatography of Matsuoka-2 et al. in the method of albumin purification by Goodey et al. and Matsuoka-1 et al. The motivation to do so, provided by Matsuoka-2 et al., would have been that α_1-acid glycoprotein was an impurity having immunosuppressive activity (col. 1, lines 44-46). Therefore, removing α_1-acid glycoprotein from albumin solution according to Matsuoka-2 et al. enhances the ability of Goodey et al. and Matsuoka-1 et al. to obtain highly purified albumin for therapeutic treatments (Goodey et al., page 1, lines 1-25).

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have repeated the AE steps in the albumin purification method of Goodey et al., Matsuoka-1 et al. and Matsuoka-2 et al. according to Chang. The motivation to do so, provided by Chang, would have been that repeating AE steps resulted in albumin purity of greater than 99% (page 4, lines 44-46).

13. Claims 116-121, 130-133, 143-145, 150 and 151 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodey et al. (WO 97/31947; cited in the IDS and in the previous office action) and of Matsuoka et al. (EP 0 428 758; cited in the IDS) (as evidenced by Cohn et al. (J. Am. Chem. Soc., vol. 68, pp. 459-475, 1946), Shaklai et al. (J. Biol. Chem., vol. 259, pp. 3812-3817, 1984; cited in the previous office action) and Ohmura et al. (EP 0 570 916 A2; cited in the IDS and in the previous office action)).

A) Teachings of Goodey et al., Matsuoka et al., Cohn et al., Shaklai et al. are presented above. Matsuoka et al. teach the concentration of albumin subjected to cation exchange chromatography being about 20 g/L, but do not specifically teach albumin concentrations of 20-70 g/L (claims 122 and 126) or albumin concentration of 50 ± 10 g/L (claims 123 and 127).

B) Optimization of conditions for performing a process is considered to be a routine experimentation and differences in conditions as compared to prior art do not support patentability of the process (see MPEP 2144. 05 IIA):

MPEP 2144.05

II. OPTIMIZATION OF RANGES

A. Optimization Within Prior Art Conditions or Through Routine Experimentation Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); >see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.");< ** In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Thus, an ordinary practitioner would have recognized that the results optimizable variable of albumin concentration subjected to cation exchange chromatography could be adjusted to maximize

the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of specific albumin concentration around 20 g/L was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the results of Matsuoka-1 et al.

14. Claims 122, 123, 126, 127, 146 and 148 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodey et al. (WO 97/31947; cited in the IDS and in the previous office action) and Matsuoka-1 et al. (EP 0 428 758; cited in the IDS) (as evidenced by Cohn et al. (J. Am. Chem. Soc., vol. 68, pp. 459-475, 1946)) and Shaklai et al. (J. Biol. Chem., vol. 259, pp. 3812-3817, 1984; cited in the previous office action)) and Matsuoka-2 et al. (U.S. Patent No. 5,277, 818), as applied to claims 82 and 86 above.

A) Teachings of Goodey et al., Matsuoka-1 et al., Cohn et al., Shaklai et al. and Matsuoka-2 et al. are presented above. Matsuoka-1 et al. teach the concentration of albumin subjected to cation exchange chromatography being about 20 g/L, but do not specifically teach albumin concentrations of 20-70 g/L (claims 122 and 126) or albumin concentration of 50 ± 10 g/L (claims 123 and 127).

B) Optimization of conditions for performing a process is considered to be a routine experimentation and differences in conditions as compared to prior art do not support patentability of the process (see MPEP 2144. 05 IIA):

MPEP 2144.05

II. OPTIMIZATION OF RANGES

A. Optimization Within Prior Art Conditions or Through Routine Experimentation

Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); >see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.");< ** In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Thus, an ordinary practitioner would have recognized that the results optimizable variable of albumin concentration subjected to cation exchange chromatography could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of specific albumin concentration around 20 g/L was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the results of Matsuoka-1 et al.

15. Claims 124, 125, 128, 129, 147 and 149 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodey et al. (WO 97/31947; cited in the IDS and in the previous office action) and Matsuoka-1 et al. (EP 0 428 758; cited in the IDS) (as evidenced by Cohn et al. (J. Am. Chem. Soc., vol. 68, pp. 459-475, 1946) and Shaklai et al. (J. Biol. Chem., vol. 259, pp. 3812-3817, 1984; cited in the previous office action)), Matsuoka-2 et al. (U.S. Patent No. 5,277, 818) and Chang (EP 0 422 769 A1; cited in the IDS and in the previous office action).

A) Teachings of Goodey et al., Matsuoka-1 et al., Cohn et al., Shaklai et al., Matsuoka-2 et al. and Chang are presented above. Matsuoka-1 et al. teach the concentration of albumin subjected to cation exchange chromatography being about 20 g/L, but do not specifically teach albumin concentrations of 20-70 g/L (claims 124 and 128) or albumin concentration of 50 ± 10 g/L (claims 125 and 129).

B) Optimization of conditions for performing a process is considered to be a routine experimentation and differences in conditions as compared to prior art do not support patentability of the process (see MPEP 2144. 05 IIA):

MPEP 2144.05

II. OPTIMIZATION OF RANGES

A. Optimization Within Prior Art Conditions or Through Routine Experimentation Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are

> disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); >see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.");< ** In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Thus, an ordinary practitioner would have recognized that the results optimizable variable of albumin concentration subjected to cation exchange chromatography could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of specific albumin concentration around 20 g/L was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the results of Matsuoka-1 et al.

16. No claims are allowed.

Conclusion

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E. Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Teresa E Strzelecka
Primary Examiner
Art Unit 1637

Teresa Strzelecka
8/4/06